Trophoblast differentiation of human ES cells.

Grant Award Details

Trophoblast differentiation of human ES cells.

Grant Type: SEED Grant

Grant Number: RS1-00283

Investigator:

Name:	Robert Oshima
Institution:	Sanford-Burnham Medical Research Institute
Type:	PI

Disease Focus: Fertility

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $696,354

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Trophoblast differentiation of human ES cells.

Public Abstract:

Human embryonic stem (ES) cells have the potential to form any cell type, but ironically, the first cell lineage to form during development still represents a surprising challenge. The first cell type to become specialized is an epithelial cell that later defines the boundary between the embryo and mother for the formation of the placenta. The placenta is the key organ that permits the blood of the mother to provide oxygen and nutrients to the fetus. It is composed of multiple cell types that are specialized for different functions but most of the fetal contributions are derived from the trophoblast cell lineage. Nearly 3% of human pregnancies are threatened by deficiencies of the function of the placenta to provide sufficient blood flow. This condition can result in dangerous increases in the mother's blood pressure that threaten the health of both the mother and fetus. Studying the molecular details of the formation and function of the different cell types of the placenta is fundamentally medically important and biologically profound as placental development is a key process that helps defines the human species.

To fully utilize the potential of ES cells, we will start with an understanding of the homogeneity and possible bias in the differentiation fate of available human embryonic stem cell lines. We will characterize multiple human ES cell lines with regard to the types of proteins that form the internal cytoskeleton of the cells. These intermediate filament proteins are widely used for identifying cells of specific tissues. One of these may be characteristic of cells that generate the trophoblast lineage. We will confirm this by comparison with the simultaneous expression of a key determinant of trophoblast cells. To facilitate this analysis we will generate a human ES cell line with a colored marker protein when it changes to the trophoblast lineage. This line will permit the detection and purification of cells choosing this fate.

In mice a trophoblast stem cell has been isolated that is capable of self renewal and retains the capability of from different cell types of the placenta but not the embryo. In mice these cells have been experimentally generated by forced temporary expression of genes capable of triggering the specification of this lineage. However, this has not yet been successful with human ES cells. We propose to isolate trophoblast stem like cells by forcing the expression of genes in human embryonic stem cells that may be expressed at insufficient levels to trigger and maintain the trophoblast stem cell and by inhibiting the late stage differentiation of the same cells. The routine isolation of trophoblast cells from human ES cells will a valuable tool for identifying targets for modulation of placenta formation and function.

Statement of Benefit to California:

This research will contribute to the application of stem cell biology to the health of persons in California by providing additional screening criteria for different hESC lines. Until recently, the routine growth of hESC from single cells was challenging. The consequences of this are that differentiated cells, or cells selected for the ability to grow under non optimal conditions may accumulate in the populations of continuously cultivated hESC. Routine purification and expansion from single cells is standard microbiological practice for virus, bacteria and cell culture. Screens that can be applied to hESC lines to better characterize their homogeneity and monitor their quality are needed, particularly as new hESC lines are isolated and applications to patient use become imminent. The first part of this proposal will contribute to the quality control of hESC lines and provide tools for the identification of differentiated cells.

The second part of the proposal will attempt to generate a unique research resource for studying the formation and function of the multiple cell types that compose the placenta. Understanding the cellular and molecular basis of "poor placentation" has not received attention proportional to the frequency of occurrence during pregnancy because of the paucity of amenable experimental systems, the current keen competition for research support and the bias toward immediate disease application. The development of extraembryonic tissues, has historically not been the focus of most developmental biologists. Medical research has concentrated on tissues and cells from term patients. The routine isolation of multipotent trophoblast cells from hESCs would provide a new avenue of research that could identify new methods or strategies of improved maternal and fetal health.

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